Anticoagulation for venous thromboembolism

Longer duration of treatment does not reduce risk of recurrence unless continued indefinitely

The optimal duration of anticoagulant therapy for the treatment of venous thromboembolism has been the subject of many randomised trials over the past 15 years. The results indicate no clear advantage for many patients of prolonging warfarin beyond three to six months, because of the risk of bleeding and the inconvenience. The annual incidence of major bleeding in patients who take warfarin for longer than three months is 2-3%, with an estimated case fatality rate of 9.1% (95% confidence interval 2.5% to 21.7%).

Also, duration of treatment has little effect on the long term risk (after the first three months) of recurrence. Trials have shown that the frequency of recurrence at two to three years is similar in patients taking three months or 12 months of oral anticoagulation. Whether the frequency of recurrence would be the same after longer lengths of treatment and follow-up is not known. Consequently, the optimal duration of oral anticoagulant treatment remains a contentious issue.

In this week’s BMJ, a randomised controlled trial by Campbell and colleagues investigates the optimal duration of oral anticoagulant treatment. It compared three or six months of warfarin (target international normalised ratio 2.0-3.5) after an initial five days of heparin in 749 patients with suspected or confirmed venous thromboembolism without ongoing risk factors for recurrence. After 12 months, recurrent fatal or non-fatal venous thromboembolism occurred in 8% of patients in each treatment group (difference 0%, −3.1% to 4.7%, P=0.80). Major bleeding occurred in significantly more patients taking warfarin for six months than for three months (2% v 0%; difference 2%, 0.7% to 3.5%, P=0.008).

The trial was discontinued prematurely because of slow recruitment, but the results provide no evidence of benefit and clear evidence of harm (bleeding) of longer duration of treatment. These results are consistent with other studies and a meta-analysis of individual patient data, which found similar frequencies of recurrence after discontinuing warfarin in patients given at least three months of anticoagulants.

The meta-analysis of individual patient data from five randomised trials compared different durations of anticoagulant treatment for venous thromboembolism, and confirmed the results of randomised trials that continuing treatment beyond three to six months does not reduce the risk of recurrence after warfarin is stopped. Each trial consistently showed a cluster of recurrences immediately after stopping treatment. The reasons for this are unknown, but possible explanations include hypercoagulability of the blood as a result of stopping warfarin or a continuing thrombotic state in some patients.

On the basis of current evidence how should we treat our patients? Patients with a first episode of venous thromboembolism should receive warfarin for at least three months. The exception is patients with isolated distal vein thrombosis, in whom six weeks is generally adequate.

Although long term treatment is highly effective for preventing recurrence in patients with unprovoked venous thromboembolism, a “catch-up phenomenon” occurs after warfarin is stopped, suggesting that long term warfarin does not alter the natural history of the disease. Because of this catch-up phenomenon, there is little point continuing treatment beyond three to six months, unless a continuing reversible risk factor exists, in which case treatment is continued until the risk is no longer present or a decision is made to continue treatment indefinitely. A decision to treat a patient indefinitely is reasonable in patients with a very high risk of recurrence, such as those with more than one episode of unprovoked thrombosis, those with cancer and thrombosis, and those with high risk thrombophilia. Indefinite treatment might also be considered in patients with severe post-thrombotic syndrome and in those with a strong preference for minimising their risk of recurrence by continuing anticoagulants.

Because it is thought that long term warfarin yields a net benefit for patients at highest risk of recurrence and that stopping warfarin is reasonable in those with a low risk of recurrence, efforts have been directed towards identifying clinical and laboratory markers that better predict the recurrence risk. Ultimately, however, the question of which patients should be treated with anticoagulants indefinitely will require large randomised studies that have sufficient power to show a worthwhile reduction of morbidity or mortality, or an improvement in quality of life.
Conduct disorders in children

Parent programmes are effective but training and provision are inadequate

In this week’s *BMJ*, Hutchings and colleagues report a randomised controlled trial and a cost effectiveness analysis of a preventive intervention in parents of preschool children at risk of developing conduct disorder. The Incredible Years basic parenting programme was offered for 12 weeks in 11 socially disadvantaged Sure Start areas. The programme significantly improved antisocial behaviour as measured by the Eyberg child behaviour inventory (difference 4.4 points, 95% confidence interval 2.0 to 6.8, effect size 0.66). The cost was between £1300 (€1900; $2500) and £2000 per child, which is comparable to most psychological treatments and a fraction of the long term cost to society of untreated conduct disorder, which is 10 times that of controls. The study shows that effective community level prevention is possible using regular service staff if they are properly trained in an evidence based programme.

Conduct disorder is a major health and social problem. It is the most common psychiatric disorder in childhood, with a prevalence of around 5% across the world, which is rising. The diagnosis is given to children who display persistent severe antisocial behaviour such as tantrums, verbal and physical aggression, lying, stealing, and violations of other people’s rights. Although the greatest damage to society is done by delinquent adolescents, the disorder usually starts below the age of 7 years with the oppositional defiant subtype.

Ineffective parenting and poor disciplinary practices at home and at school are major determinants of this disorder, which has widespread effects on many levels of society. The management of this disorder requires input from the education sector, social services, and the police. The health service should be involved too, for several reasons. Firstly, there is a substantial genetic influence on the causation of conduct disorder; secondly, it is often associated with neuropsychological disorders, such as attention deficit hyperactivity disorder; thirdly, the disorder has physical health consequences such as increased accidents and higher suicide rates; and finally, mental health professionals have led the way in developing effective assessment and treatments.

Last year the National Institute for Health and Clinical Excellence (NICE) released a health technology assessment on the effectiveness of parent training and education programmes for the treatment of conduct disorders in children. This year, the UK government will launch a new National Academy for Parenting Practitioners.

The health technology assessment recognised the need for wider involvement and was jointly commissioned with the Social Care Institute for Excellence. Based on a meta-analysis of 37 randomised controlled trials, it concluded that parent training programmes seem to be effective. The mean effect size was close to 0.8 standard deviations on parent report measures and 0.5 standard deviations on direct observation. These effects are of the same order of magnitude as for antidepressants in adults. The assessment is misleading, however: it states that the trials were “of poor quality” only because they did not report their methods of randomisation or concealment in detail, something which has not been the tradition in psychology journals. In fact, all the trials were randomised (usually by reputable university statisticians) and most used high quality methods and measures, so their conclusions are sound. In future, NICE should contact trial authors for this missing information. The report also urges caution because most trials were from the United States, yet there have been several UK studies showing similar effectiveness.

Future research should investigate the long term effectiveness of parenting programmes; which aspects of parenting need to be changed (both a reduction in negative parenting and an increase in positive parenting seem to mediate changes in children’s behaviour), which techniques are most effective; and what modifications, including compulsory attendance orders, are needed to reach the most disorganised and abusive families.

Health commissioners and providers have far to go in delivering the quantity and quality of services needed. Currently, only a quarter of children with conduct disorder receive specialist treatment, which may not be delivered according to NICE guidelines, as fewer than 1000 practitioners are trained in programmes recommended by NICE. It is unlikely that such failure to provide most patients with effective treatment would be tolerated for a physical condition such as childhood asthma, yet the long term morbidity and quality of life are probably at least as bad in conduct disorder.

Within existing National Health Service provision, the health technology assessment may begin to shift practice, but NICE should now commission practice guidelines for assessing and treating conduct disorder. As well as parenting programmes, child anger management and problem solving treatments can be effective; the value of medication is dubious. A major problem for expanding provision of parenting programmes is that postgraduate courses in psychology and psychiatry have limited capacity for training in behaviourally based methods. Consequently, much training is carried out by producers of commercially marketed programmes, which although usually of high quality are short (typically three days) and cover only one particular approach.

Cross governmental responsibility for severe antisocial behaviour was recognised in the “respect” agenda launched by the prime minister last year. This included plans for a National Academy of Parenting Practitioners, which will oversee training of the parenting workforce across statutory, voluntary, and private sectors. It remains to be seen whether the academy will be able to persuade practitioners outside the health service to adopt effective practices. But if the health technology assessment and the academy lead to the dissemination of high quality, evidence based approaches they could have a major impact on children’s health and wellbeing by improving the outlook for those with conduct disorder.
Acute coronary syndrome

Glycoprotein inhibitors are still underused, especially in patients at high risk

About 120 000 people are diagnosed with acute coronary syndrome in England and Wales each year, and about 1.5 million people are discharged from hospitals in the United States with the diagnosis. Despite the use of standard medical treatment, the risk of death or non-fatal myocardial infarction is about 10% within 30 days, and the proportion of adverse outcomes is about 30% at six months.

Doctors who deal with acute medical admissions are well accustomed to the diagnosis and initial medical management of acute coronary syndromes. However, many doctors are less confident about the use of glycoprotein IIb/IIIa inhibitors, such as eptifibatide and tirofiban, in these patients and often await a cardiology review. This may be less important in tertiary centres where a specialist opinion is prompt and patients at high risk are quickly identified and stratified to invasive strategies or coronary care units. In district general hospitals, however, the admitting doctor decides which patients could benefit from more aggressive strategies. This is especially true out of normal working hours, when the cardiology team is not available. Moreover, recent data from the myocardial infarction national audit project suggest that most patients with acute coronary syndrome are initially managed by non-cardiologists on acute wards.

Glycoprotein IIb/IIIa inhibitors inhibit the final common pathway of platelet aggregation, so they can limit the adverse effects of plaque disruption (which is central to the pathogenesis of acute coronary syndrome), over and above that of other pharmacological or physical approaches. Their value has been proved in patients who undergo percutaneous coronary interventions, as well as those not routinely scheduled for such an intervention. Pooled analysis of the use of these inhibitors in percutaneous coronary intervention found that they reduced the occurrence of composite end points by 33% compared with placebo. A further meta-analysis in patients with acute coronary syndrome not routinely scheduled for percutaneous coronary intervention found a 16% reduction in the relative risk of death or myocardial infarction at five days with glycoprotein IIb/IIIa inhibitors compared with placebo and a 9% reduction at 30 days. In a subgroup analysis, the greatest benefit was shown in patients at high risk (those with a TIMI (thrombolysis in myocardial infarction) score ≥4). A 31% lower relative risk of composite end points at 30 days was seen in the group as a whole, regardless of percutaneous coronary interventions.

In 2002, the National Institute for Health and Clinical Excellence (NICE) published guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. These guidelines state that, “Glycoprotein IIb/IIIa inhibitors are recommended as part of the initial management of patients with unstable angina or non-ST segment elevation myocardial infarction who are at high risk of subsequent myocardial infarction or death, even in situations where percutaneous coronary intervention does not occur or is not immediately available.” This has been shown to be the most cost effective use of these agents within the National Health Service. Guidelines in the US agree that patients at high risk should receive glycoprotein inhibitors, especially if an invasive strategy is planned, but they emphasise that direct evidence with regard to quadruple therapy (aspirin, heparin, and particularly the combination of clopidogrel and glycoprotein IIb/IIIa inhibitor) is currently lacking.

Data from the Global Registry of Acute Coronary Events (GRACE) and the National Registry of Myocardial Infarction (NRMI) show that these inhibitors are under-used internationally.11 Our impression, based on local audit data and observation, is that in the UK the current guidelines are not being followed. There may be several reasons for this.

Firstly, the definition of “high risk” is open to interpretation. The factors specified by NICE (box 1) do not provide an objective measure of risk and can create uncertainty for the general physician. In our trust, we use the TIMI risk score (box 2), which has been repeatedly validated as an accurate predictor of ischaemic complications and high risk angiographic findings. It identifies patients who benefit most from aggressive management, including glycoprotein IIb/IIIa inhibitors. Other risk estimation scores are available, but TIMI is probably most widely used, especially in the US. However, in other countries acute coronary syndromes are more commonly treated by a cardiologist who will assess risk through experience, recognition of high risk changes on electrocardiography, and observation of the factors that are outlined in the NICE guidance.

A TIMI risk score of 5-7 identifies patients who are at high risk and should have early treatment with...
Erythropoiesis stimulating agents
May not be safe in people with cancer

In February 2007, new concerns surfaced over the safety of agents that stimulate erythropoiesis when used to treat anaemia in patients with cancer. These concerns quickly gained the attention of the oncology community and the popular press. Most major newspapers carried this story1 because of the widespread clinical use of these agents and the high volume of advertising by the drugs’ corporate sponsors aimed directly at the consumer.²

Safety concerns relate to the possibility that erythropoiesis stimulating agents are associated with increased tumour growth and worse survival in some patients with cancer. On 9 March 2007, a black box warning was added to the labelling of darbepoetin alfa and epoetin alfa in the United States. This instructed doctors to use the lowest dose possible to avoid red blood cell transfusions, and not to allow haemoglobin concentrations to exceed 120 g/l.³ The Food and Drug Administration has announced a special meeting of the Oncology Drugs Advisory Committee on 10 May 2007 to discuss this matter further.

Both randomised and open label trials have shown that patients with anaemia associated with cancer chemotherapy who are treated with erythropoiesis stimulating agents need fewer transfusions, have higher haemoglobin concentrations, and possibly have higher quality of life than those who are not treated.⁴ Most of the early theoretical concerns about erythropoietin’s potential to alter tumour behaviour dissipated by the time a meta-analysis in 2005 found no difference in survival with erythropoiesis stimulating agents than with supportive care alone or placebo.⁴

Two studies suggesting specific risks for cancer patients from erythropoiesis stimulating agents first appeared in 2003, but were largely dismissed because of limitations in trial design and conduct.⁵ The first study found a higher rate of tumour progression and worse survival in patients with head and neck cancer treated with epoetin beta compared with placebo.⁶ The second trial, in patients with metastatic breast cancer, was terminated early because of higher mortality in people taking epoetin alfa (8.7% ± 3.4%), a difference that became evident after only four months of treatment.⁷ These findings raised concerns—some of which focused on thromboembolism rather than tumour growth—but overall were considered inconclusive, especially given the robust safety record with epoetin accumulated over the previous decade. Importantly, the target haemoglobin range in these two studies (140-155 g/l and 120-140 g/l, respectively) was higher than that normally used with erythropoietin or recommended by professional society guidelines.⁸

In light of these results, the Oncology Drugs Advisory Committee held a meeting in 2004 and recommended label changes for epoetin alfa and darbepoetin alfa that warn about excessive rises in haemoglobin concentrations and urge specifically against trying to raise them above 120 g/l.

More recently, a growing number of studies have been terminated early or have reported worrying preliminary results, which suggests that the 2003 results were not spurious. A Danish trial of 522 patients with head and neck cancer receiving radiotherapy, which was stopped early after an interim analysis in November 2006, found a 10% increase in locoregional disease progression and a trend towards worse survival in the

Box 2 | Thrombolysis in myocardial infarction (TIMI) risk score—1 point for each characteristic

- Age ≥65 years
- At least 3 risk factors for coronary artery disease
- Known coronary artery disease (≥50% stenosis)
- Aspirin use in past 7 days
- Recent (≤24 hours) severe angina
- ST segment deviation ≥0.5 mm
- Raised cardiac markers

glycoprotein IIb/IIIa inhibitors. Patients at moderate risk (TIMI 4) should also be considered for such treatment in certain clinical situations, such as ongoing pain and high risk changes on electrocardiogram (especially if they are troponin positive). Although most doctors who admit patients record cardiac risk factors at admission, very few record high risk indicators, so high risk status is not always immediately recognised.

Secondly, it is still common for teams admitting patients to delay treatment with glycoprotein IIb/IIIa inhibitors while awaiting troponin test results. Although patients with evidence of myonecrosis benefit most from these inhibitors the NICE guidance states that, “High-risk patients should be treated with glycoprotein IIb/IIIa inhibitors as soon as high-risk status is determined even though this may be before the result of a troponin test is known.”

Thirdly, it is a misconception that glycoprotein IIb/IIIa inhibitors are useful only as a bridge to percutaneous coronary intervention. Treatment is often not started in patients who are considered unsuitable for invasive strategies. Conversely, these patients are often at high risk, as they are elderly or have other comorbidities. However, the NICE guidance states that, “In situations where percutaneous coronary intervention does not occur or is not immediately available, initial medical management with glycoprotein IIb/IIIa inhibitors is still recommended.”

It is important that admitting teams confidently assess risk status and incorporate glycoprotein IIb/IIIa inhibitors into the initial medical treatment of acute coronary syndrome. This responsibility extends to nursing staff as well as clinicians. Nurses who work on acute or emergency wards should be trained and confident in the administration of these inhibitors. In patients at high risk, treatment should not be delayed because troponin test results are not yet available. We advocate routine use of the TIMI risk score in patients with acute coronary syndrome.
Institutional racism in mental health care

Services have some way to go before they meet the challenges of a multicultural society

Last week, the Healthcare Commission reported the findings of the “Count me in” one day census of National Health Service hospitals, private mental health hospitals, and learning disability units. It makes grim reading for people of African and Caribbean origin living in England and Wales.

The survey of 32 023 inpatients on mental health wards in 238 NHS and private healthcare hospitals reported that 21% of patients were from black and minority ethnic groups, although they represent only 7% of the population. Rates of admission were lower than average in the white British, Indian, and Chinese groups, but three or more times higher than average in black African, black Caribbean, and white and black Caribbean mixed groups. Not only were people in these three groups more likely to be admitted to hospital, but those in hospital were 19.39% more likely to be admitted involuntarily. Once in hospital, people who defined themselves as black Caribbean had the longest stay.

Though high incidence rates of severe mental illness have been reported in people of African and Caribbean origin, admission rates reflect the prevalence of an illness. National community based prevalence studies have not found high rates of psychosis or other serious mental illnesses that could account for these findings. Moreover, increased incidence and prevalence of mental illness has been reported in some groups of South Asian origin, but the Count me in census does not report a corresponding increase in admission rates.

The survey of people with learning disabilities comprised 4609 inpatients from 124 hospitals. Only 11% were from black and minority ethnic groups. Rates...
discussions on whether racism is intentional rather than focusing on the disparities, thereby vindicating all inequity if no proof of intent is found. The last response is to ignore the urgency of the problem and to ask for more research, while proposing no remedial action for demonstrated disparities.

In contrast, once the existence of institutional racism in mental health care is accepted, progress can be made to understand and tackle the causes of racial disparities. For instance, it has led to the development of “Delivering race equality,” a systems level approach to improving mental health services.

Delivering race equality could improve services, but leadership is needed to ensure that it is taken up. A recent survey by the Healthcare Commission found that only a minority of trusts scored highly on its implementation. Moreover, fewer than half of the required number of community development workers—who were meant to be the backbone of improvement—have been recruited across the NHS, even though the money has been available since 2004.

Delivering race equality may have some impact on disparities in involuntary admissions, but because such admissions reflect the combined actions of the criminal justice system, social services, and education, a strategy based in mental health services alone is unlikely to be sufficient. There is also a danger that its impact will be undermined by other government policy. The proposed amendments to the Mental Health Bill that are making their way through parliament are likely to increase disparities in involuntary admission rates for black and minority ethnic groups, and the government has largely ignored its advisers on this subject.

There are also wider questions about whether treatment is being offered and delivered effectively. It is surprising that, despite the race relations amendment act, National Institute for Health and Clinical Excellence guidelines do not have a formal impact assessment for race equality. It is unclear whether practitioners following these guidelines are offering culturally competent care.

The Count me in census and other research indicate that institutional discrimination does occur and that services have some way to go before they meet the challenges of our multicultural society. Delays in setting up ways to deal with disparities, delays in implementing guidance, and delays in developing appropriate and responsive services cause institutional racism.

People who think that claims of institutional racism may harm patient care should be aware that until disparities and remedial action were seen through this lens no strategy existed for improving mental health services for black and minority ethnic groups. If the concept of institutional racism had been more widely accepted and acted on, the Department of Health might not now be facing a formal investigation by the Commission for Racial Equality.

Box | Definition of institutional racism
The collective failure of an organisation to provide an appropriate and professional service to people because of their colour, culture, or ethnic origin. This can be seen or detected in processes, attitudes, and behaviour that amount to discrimination through unwitting prejudice, ignorance, thoughtlessness, and racist stereotyping which disadvantages people in ethnic minority groups.